Phosphate Binders
Therapeutic Class Review (TCR)

November 7, 2017

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
calcium acetate (Eliphos®)[1]	generic, Hawthorn	Phosphate binder indicated to reduce serum phosphorus in adult with end stage renal disease (ESRD)
calcium acetate[2]	generic	Phosphate binder indicated for the reduction of serum phosphorus in adult with ESRD
calcium acetate (Phoslyra®)[3]	Fresenius Medical Care	Phosphate binder indicated to reduce serum phosphorus in adult with ESRD
ferric citrate (Auryxia™)[4]	Keryx Biopharmaceuticals	Phosphate binder indicated for the control of serum phosphorus levels in adults with chronic kidney disease (CKD) on dialysis Iron replacement product for the treatment of iron deficiency anemia in adults with CKD not on dialysis
lanthanum carbonate (Fosrenol®)[5]	generic, Shire US	Phosphate binder indicated to reduce serum phosphate in adults with ESRD
sevelamer carbonate (Renvela®)[6]	generic, Genzyme	Phosphate binder indicated for the control of serum phosphorus in patients ≥ 6 years of age with CKD on dialysis
sevelamer hydrochloride (Renagel®)[7]	Genzyme	Phosphate binder indicated for the control of serum phosphorus in adults with CKD on dialysis
sucroferric oxyhydroxide (Velphoro®)[8]	Fresenius Medical Care	Phosphate binder indicated for the control of serum phosphorus in adults with CKD on dialysis

*Generic for PhosLo® by Fresenius Medical Care; the brand has since been discontinued.

OVERVIEW

Chronic kidney disease (CKD) affects approximately 30 million Americans in the United States (U.S.).[9] As kidney function deteriorates, the ability to eliminate phosphorus declines, resulting in hyperphosphatemia, one of the complications of CKD. Elevated levels of phosphorus inhibit the conversion of 24-hydroxyvitamin D to 1,25-dihydroxyvitamin D (calcitriol). The reduction in calcitriol decreases intestinal absorption of calcium and eventually leads to hypocalcemia. In end stage renal disease (ESRD), patients are at risk for several complications of hyperphosphatemia, including the development of renal bone disease and extraosseous calcifications of soft tissue and vasculature. Hyperphosphatemia (> 6.5 mg/dL) is also associated with increased risk of death.[10,11,12,13]

Direct stimulators of parathyroid hormone (PTH) secretion include hypocalcemia, low levels of calcitriol, and hyperphosphatemia. Secondary hyperparathyroidism contributes to abnormal bone metabolism observed in CKD. Management of renal osteodystrophy includes maintenance of calcium and phosphate balance, vitamin D supplementation, reduction of patient exposure to aluminum, and, in some cases, parathyroidectomy.

Hyperphosphatemia is a risk factor for cardiovascular disease (CVD).[14] Studies have also shown an increased risk of mortality in patients with CKD stage 5D with hyperphosphatemia. Data suggest the need to control serum phosphorus in patients with CKD. Long-term hyperphosphatemia along with elevated calcium x phosphorus (Ca X P) values (≥ 55 mg^2/dL^2) is linked to an increased risk of vascular, valvular, and other soft tissue calcification in patients with CKD. Soft tissue calcifications occurring in vascular and cardiac tissue can lead to increased morbidity and mortality.[15,16] Patients with elevated Ca

X P values are at a significantly higher risk of death.[17] The Ca X P product is calculated by using the patient's corrected serum calcium level and serum phosphorus level.

The National Kidney Foundation released guidelines in 2009 titled the Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD) and updated these guidelines in 2017 under The Kidney Disease: Improving Global Outcomes (KDIGO) foundation.[18] Treatment of hyperphosphatemia includes the reduction of dietary phosphorus, phosphate binding therapy, and removal of phosphorus by dialysis and should consider serial phosphate, calcium, and PTH levels. The guidelines recommended lowering serum phosphate levels in patients with CKD stages 3a through 5D toward the normal range (grade 2C) and avoiding hypercalcemia in adults (grade 2C) and maintaining age-appropriate serum calcium in pediatrics (grade 2C). However, the guidelines state there is no evidence that lowering serum phosphorus to a specific target range leads to improved clinical outcomes, and goals of therapy should be based on observational data. Although the recommendation is not graded, they recommend basing decisions regarding phosphate-lowering treatment on progressively or persistently elevated serum phosphate rather than to prevent hyperphosphatemia. They further recommend restricting the dose of calcium-based phosphate binders adults with CKD stages 3a through 5D (grade 2B) and that the choice of phosphate-lowering therapy should be based on serum calcium levels in children with CKD stages 3a through 5D (not graded). They recommend avoiding long-term use of aluminum-containing phosphate binders in these patients and avoiding dialysate aluminum contamination in patients with CKD stage 5D to avoid aluminum intoxication (grade 1C).

The KDIGO 2012 clinical practice guidelines for the evaluation and management of CKD suggest that adult patients and pediatric patients with CKD stage 3 (recommendation 1C) and CKD stage 2 (recommendation 2D), respectively, should have their levels of calcium, phosphorus, PTH, and alkaline phosphatase activity monitored.[19] The frequency of monitoring depends on identified abnormalities, glomerular filtration rate (GFR) severity and abnormalities, and use of concomitant medications. It is also recommended that patients with stage 3 to 5 CKD, with and without dialysis, maintain phosphorus levels within normal range as numerous epidemiological studies show a positive correlation between higher serum phosphorus levels and relative risk of mortality, independent of CKD stage, as well as an increased risk for bone disease, vascular calcification, and cardiovascular disease. The guidelines recommend that patients with CKD stages 3 to 5 (recommendation 2D) and CKD stage 5D (dialysis; recommendation 2B) use phosphate-binding agents for the treatment of hyperphosphatemia. Studies have shown that all phosphate lowering medications (e.g., calcium salts, aluminum salts, magnesium salts, sevelamer HCl, and lanthanum carbonate) are effective in lowering serum phosphorus levels. In patients with CKD stages 3 to 5D and hyperphosphatemia, the guidelines suggest restricting the dose of calcium-based phosphate binders in the presence of persistent or recurrent hypercalcemia (recommendation 1B), arterial calcification (recommendation 2C), adynamic bone disease (recommendation 2C), and serum PTH levels that are persistently low (recommendation 2C). In patients with CKD stages 3 to 5D, the guidelines strongly recommend avoiding the long-term use of aluminum containing phosphate binders, as they may cause neurotoxicities and impair bone mineralization, and there is also no ability to predict a safe aluminum dose. Overall, the updated guidelines note there is insufficient comparative efficacy data on clinical outcomes to endorse the use or superiority of 1 phosphate binder medication over another. The selection of an appropriate phosphate binder should be individualized and based on various clinical parameters, not phosphorus lowering alone. In 2014, NKF-Kidney Disease Outcomes Quality Initiative (KDOQI) published

commentary on the 2012 KDIGO CKD guidelines.[20] Overall, the commentary agreed with most of the guideline statements especially the definition and classification of CKD; however, concerns were raised regarding the inclusion of cause of disease into CKD classification and certain recommendations for evaluation and management. Sucroferric oxyhydroxide (Velphoro) and ferric citrate (Auryxia) were not available at the time this guideline was developed.

Over-the-counter calcium acetate (Calphron® OTC) is a dietary supplement that binds dietary phosphate.[21] It is a tablet that contains 667 mg of calcium acetate. MagneBind® 400 Rx is a prescription dietary supplement with an off-label indication of hyperphosphatemia and nutritional supplementation.[22,23] It is a tablet of calcium carbonate 200 mg, folic acid (vitamin B9) 1 mg, and magnesium carbonate 400 mg. Calphron OTC and MagneBind 400 Rx will not be included in this review as they are dietary supplements.

Anemia and iron deficiency are often associated with CKD, including in patients who are not dependent on dialysis.[24] Anemia is associated with mortality,cardiovascular events, and decreased quality of life. Further, untreated iron deficiency can impact response to treatment with erythropoiesis-stimulating agents (ESA).[25] The 2012 KDIGO guidelines on anemia related to CKD recommend that the route of iron administration be selected based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects to prior oral or intravenous iron treatment, patient compliance, and cost; subsequent doses should be guided by hemoglobin response, iron status, response to ESA, and ongoing blood losses. In 2017, ferric citrate (Auryxia) was approved as an iron replacement product for the treatment of iron deficiency anemia in adults with CKD not on dialysis. Use of ferric citrate for iron deficient anemia related to CKD is not addressed in these guidelines.

PHARMACOLOGY[26,27,28,29,30,31,32,33]

Efforts to control hyperphosphatemia include a reduction in dietary intake of phosphate, inhibition of phosphate absorption via phosphate binders, and removal of phosphate through dialysis methods. Dialysis patients absorb 40% to 80% of their dietary phosphorus and often the rate of phosphate removal by dietary management or by dialysis is insufficient. Therefore, most renal failure patients on maintenance dialysis need to use phosphate binders in order to reduce the amount of dietary phosphate absorbed. Phosphate-binding agents decrease phosphorus absorption from the gastrointestinal (GI) tract by binding dietary phosphorus. Maintaining serum phosphorus below 6 mg/dL is generally considered a clinically acceptable outcome of treatment with phosphate binders.

Calcium-containing salts (Eliphos, PhosLo generics, and Phoslyra) not only maintain positive calcium balance but also bind with dietary phosphorus to create an insoluble calcium phosphate complex which is then eliminated through the feces. This process decreases the serum phosphorus concentration. Calcium and vitamin D analog supplementation may be necessary to slow or prevent renal bone disease.

Five non-calcium phosphate binders are now available and offer an alternative to calcium-based agents when hypercalcemia is present. Sevelamer (Renagel, Renvela) is a non-calcium, non-aluminum, non-magnesium, non-absorbable hydrogel that binds phosphorus. Sevelamer is available in 2 salt forms – sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela). Sevelamer produces a similar reduction in serum phosphorus levels as calcium acetate, but it is less likely to induce hypercalcemia. Another phosphate-binding agent is lanthanum carbonate (Fosrenol). Lanthanum is a naturally occurring earth element with a high affinity for phosphorus. Lanthanum binds with phosphorus to form

insoluble lanthanum phosphate.[34] The diminished absorption of dietary phosphate reduces serum phosphate and calcium phosphate levels. Sucroferric oxyhydroxide (Velphoro) is a mixture of polynuclear iron (III)-oxyhydroxide, sucrose, and starches. Phosphate binding takes place by ligand exchange between hydroxyl groups and/or water in sucroferric oxyhydroxide and dietary phosphate in the aqueous environment of the GI tract. The bound phosphate is eliminated through the feces which in turn reduces serum phosphorus and calcium-phosphorus product levels. Ferric citrate (Auryxia) contains ferric iron which binds dietary phosphate in the GI tract and precipitates as ferric phosphate. Ferric phosphate is not absorbed and excreted in the stool, thereby decreasing the body's phosphate absorption and serum concentrations.

PHARMACOKINETICS[35,36,37,38,39,40,41,42]

Absorption rate of calcium is dependent on numerous factors including the presence of vitamin D. Bioavailability of calcium acetate is 30% to 40%.

Sevelamer is not absorbed and is excreted in the feces. Sevelamer also reduces low-density lipoprotein (LDL-C) and total cholesterol by 15% to 31%. Absorption of fat soluble vitamins may be reduced as sevelamer binds to bile acids and interferes with fat absorption.

Lanthanum carbonate has an extremely low bioavailability (< 0.002%) and is primarily excreted in the feces.[43] Lanthanum carbonate dissociates in the upper GI tract to release lanthanum ions that bind phosphate from food. Lanthanum forms insoluble complexes with phosphate that are eliminated via the feces. Systemic exposure to lanthanum was approximately 30% higher after administering lanthanum oral powder compared to lanthanum chewable tablets. However, systemic exposure from both formulations in the study was within the range seen in prior studies of the chewable tablets.

The active moiety of sucroferric oxyhydroxide, polynuclear iron (III)-oxyhydroxide, is virtually insoluble and not absorbed or metabolized; therefore, no pharmacokinetic studies have been performed.

Formal pharmacokinetic studies have not been performed with ferric citrate (Auryxia). However, serum iron parameter examinations have shown systemic absorption of iron.

CONTRAINDICATIONS/WARNINGS[44,45,46,47,48,49,50,51]

Calcium acetate (PhosLo generics, Eliphos, and Phoslyra) should not be administered in the presence of hypercalcemia. Additionally, calcium supplements should be avoided when using calcium acetate. Patients with ESRD are at increased risk of developing hypercalcemia when treated with calcium acetate. Chronic hypercalcemia could lead to complications, such as vascular calcification and other soft-tissue calcifications. The serum Ca X P product should not exceed 55 mg^2/dL^2. If hypercalcemia develops, the dosage should be reduced or discontinued depending on the severity. Decreasing or discontinuing vitamin D therapy is advised, as well. If severe, acute hemodialysis may be needed. Calcium acetate therapy should be started at a low dose and increased with careful monitoring. Serum calcium should be monitored twice weekly early in treatment and serum phosphorus should also be monitored. In addition, hypercalcemia may aggravate digitalis toxicity. In the event of hypocalcemia, calcium supplementation and/or vitamin D sterols should be administered.

Sevelamer is contraindicated in the presence of bowel obstruction and in patients with known hypersensitivity to sevelamer or any of the excipients. Safety and efficacy of sevelamer in patients with dysphagia, swallowing disorders, and severe GI motility disorders, including severe constipation or

major GI tract surgery, have not been established. Caution should be exercised when sevelamer is used in patients with these GI disorders. Dysphagia and esophageal tablet retention have been reported with the use of sevelamer tablets. Consider using sevelamer suspension in patients with swallowing disorders. Bowel obstruction and perforation have been reported with sevelamer use. Patients should have the following levels monitored while using sevelamer: bicarbonate, chloride, folic acid, and vitamins D, E, and K.

Lanthanum is contraindicated in bowel obstruction, ileus, and fecal impaction. Reports of serious cases of GI obstruction, ileus, subileus, GI perforation, and fecal impaction have been reported in connection with lanthanum, some requiring surgery or hospitalization. Risk factors for GI obstruction and perforation include alteration in GI anatomy (e.g., colon cancer, history of GI surgery, GI ulceration); hypomotility disorders (e.g., constipation, ileus, subileus, diabetic gastroparesis); and concomitant medications (e.g., calcium channel blockers). However, some cases of GI obstruction were reported in patients with no history of GI disease. Patients are advised to thoroughly chew the tablet to reduce the risk of adverse GI events. If a patient has poor dentition, it is recommended that lanthanum be crushed thoroughly prior to administration or the oral powder formulation be used. Abdominal x-rays of patients taking lanthanum may have a radio-opaque appearance typical of an imaging agent. Patients with ulcerative colitis, acute peptic ulcer, Crohn's disease, or bowel obstruction were not included in lanthanum clinical studies. Caution should be used in patients with these conditions taking lanthanum.

Sucroferric oxyhydroxide (Velphoro) has no known contraindications. Patients with peritonitis during peritoneal dialysis, a history of hemochromatosis or other iron accumulation diseases, or significant gastric or hepatic disorders following gastrointestinal surgery, have not been included in clinical studies. Patients with these disorders should be closely monitored for medication effects and iron homeostasis.

Ferric citrate (Auryxia) is contraindicated in patients with iron overload syndromes due to the medication increasing iron absorption which could lead to increased serum iron and excessive increases in iron stores. Iron parameters (e.g., serum ferritin, transferrin saturation [TSAT]) should be assessed prior to initiating therapy and thereafter. The medication should also be kept away from children as it could cause fatal poisoning in children under 6 years old. Patients receiving intravenous iron may need a dose reduction or discontinuation of intravenous iron therapy.

DRUG INTERACTIONS[52,53,54,55,56,57,58,59]

Very limited drug interaction studies were performed with the agents in this review. For oral medications where a reduction in the bioavailability of the medication could cause a clinically significant effect on its safety or efficacy, consider separating the administration times based upon the pharmacokinetics of the medications (e.g., absorption characteristics, time to reach peak systemic levels) and whether the medication is an immediate- or extended-release product. Monitoring blood levels of narrow therapeutic index drugs when taken concurrently with these products is recommended.

Calcium acetate (Eliphos, Phoslyra, generic) may reduce the bioavailability of tetracyclines and fluoroquinolones (approximately 50%) since the medication binds to drugs with anionic function. Fluoroquinolones should be taken at least 2 hours before or 6 hours after calcium acetate; tetracyclines should be taken at least 1 hour before calcium acetate; and levothyroxine should be taken at least 4 hours before or after calcium acetate.

Sevelamer (Renvela, Renagel) does not interact with digoxin, warfarin, enalapril, metoprolol, or ferrous sulfate.[60,61] Sevelamer should be dosed separately from ciprofloxacin (taken at least 2 hours before or 6 hours after sevelamer; coadministration decreases ciprofloxacin bioavailability by 50%) and mycophenolate (taken at least 2 hours before sevelamer; coadministration decreases mycophenolate bioavailability by 36% and 26% in adults and pediatrics, respectively).

Lanthanum (Fosrenol) has the potential to bind to anionic groups in medications. The bioavailability of tetracyclines or fluoroquinolones may also decrease with concurrent use of lanthanum via this mechanism. In a single dose study of ciprofloxacin and lanthanum, a reduction of > 50% of the absorption of ciprofloxacin was observed with concurrent administration.[62] Therefore, oral quinolones should be administered at least 1 hour before or 4 hours after lanthanum. Do not take thyroid hormone replacement therapy within 2 hours of dosing with lanthanum as bioavailability of thyroid hormones may decrease by up to 40%. Monitoring of TSH levels is recommended in patients receiving both medicinal agents. As a general precaution, drugs which interact with antacids should be administered at least 2 hours before or after lanthanum. Lanthanum does not interact with the CYP450 enzyme system.

No data are available on avoiding drug interactions when sucroferric oxyhydroxide (Velphoro) is taken with other oral medications. However, it is recommended that doxycycline should be taken at least 1 hour prior to administration and levothyroxine should not be prescribed along with sucroferric oxyhydroxide.

No data exist on avoiding drug interactions with ferric citrate (Auryxia) and most other oral medications; therefore, timing of administration may be important when used concomitantly with medications where changes in bioavailability could have significant effects. However, it is known that doxycycline should be taken at least 1 hour before ferric citrate, and ciprofloxacin should be taken at least 2 hours before or after ferric citrate. When coadministered with narrow therapeutic medications, monitoring of clinical responses and blood levels may be required.

ADVERSE EFFECTS[63,64,65,66,67,68,69,70]

Drug	Hypercalcemia	Diarrhea	Constipation	Nausea	Vomiting
calcium acetate (Eliphos)	12.6	nr	reported	3.6	2.4
calcium acetate* n=167	12.6	nr	reported	3.6	2.4
calcium acetate (Phoslyra)†	12.6	reported	nr	3.6	2.4
ferric citrate (Auryxia)	nr	21	8	11	7
lanthanum carbonate (Fosrenol) n=180	nr	reported	reported	11	9
sevelamer carbonate (Renvela)	nr	nr‡	nr‡	nr‡	nr‡
sevelamer hydrochloride (Renagel) n=99	nr	19	8	20	22
sucroferric oxyhydroxide (Velphoro)	nr	4-24	nr	2-10	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. nr = not reported.

* Generic for PhosLo by Fresenius Medical Care; the brand has since been discontinued.

† No clinical trials have been performed with Phoslyra in the intended population. Because the dose and active ingredients of Phoslyra are equivalent to that of the calcium acetate gelcaps or tablets, the scope of the adverse reactions is anticipated to be similar. Phoslyra contains maltitol (1 gram per 5 mL) and may produce laxative effects.

‡ Adverse reaction data is limited on Renvela; however, based on the fact that it contains the same active ingredient as Renagel, the adverse reaction profiles should be similar.

Calcium acetate can cause hypercalcemia; therefore, monitoring of serum calcium is suggested. Symptoms of mild hypercalcemia (calcium 10.5 to 11.9 mg/dL) may include constipation, anorexia, nausea, and vomiting. Severe hypercalcemia (calcium > 12 mg/dL) may present as confusion, delirium, stupor, and coma. A reduction in calcium supplementation and dialysis will help reduce calcium levels.[71] Dyspepsia (16%), abdominal pain (9%), and flatulence (8%) are also common adverse reactions; based on clinical trials, the most common reason for discontinuation of calcium acetate was due to GI events (3-16%).

Lanthanum deposits into bone over a period of several years. Long-term effects of lanthanum in bone are not known.[72] Paired bone biopsies (at baseline and at 1 or 2 years) in 1 study comparing lanthanum to calcium carbonate and another study comparing lanthanum to an alternative therapy showed no differences in the development of mineralization defects.[73]

In a 1-year study with 20 patients, lanthanum was shown to be deposited into bone in low concentrations.[74] After discontinuing lanthanum for 2 years, plasma and bone concentrations of lanthanum were still detectable although at lower concentrations than during active treatment. Bone biopsies from 105 patients treated for up to 4.5 years showed rising lanthanum levels. Estimated elimination half-life from bone ranged from 2 to 3.6 years.[75] A total of 22 patients have received lanthanum as a part of a clinical trial to monitor the efficacy and safety.[76] Lanthanum doses were 2,250 to 3,000 mg per day for two-thirds of the patients. Efficacy in reducing serum phosphate and Ca X P product were maintained up to 6 years. Over the complete duration of therapy, treatment-related adverse effects occurred in 25.8% of patients and were primarily GI in nature. No new adverse effects were reported; no increase in the incidence of adverse events was reported. No evidence of adverse effects on the liver, bone, or the central nervous system was observed.

In studies, lanthanum oral powder resulted in higher GI adverse reactions such as nausea, diarrhea, and vomiting compared to lanthanum chewable tablets, 18% versus 7%, respectively.

Both rash and tooth discoloration have been reported with sucroferric oxyhydroxide (Velphoro). Patients should be advised against chewing or crushing ferric citrate (Auryxia) tablets, which may lead to discoloration of the mouth and teeth.

Sucroferric oxyhydroxide may cause dark colored feces (12% to 16%), which are common with oral iron preparations. Diarrhea associated with sucroferric oxyhydroxide use occurred soon after beginning treatment but resolved with continued use of the product.

Ferric citrate is associated with dark stools related to the iron content. Cough is also a commonly reported adverse reaction (6%) in patients using ferric citrate.[77]

SPECIAL POPULATIONS[78,79,80,81,82,83,84,85]

Pediatrics

Safety and efficacy for pediatric use of agents in this class have not been established, with the exception of sevelamer carbonate (Renvela).

The safety and efficacy of sevelamer carbonate in lowering serum phosphorus levels was studied in patients ≥ 6 years of age with CKD. However, limited data suggest it may be less effective in children with a low baseline serum phosphorus. It has not been studied in pediatric patients < 6 years of age.

Calcium based phosphate binders have been effective in decreasing phosphate levels in children with CKD. However, evidence comparing newer non-calcium binders with calcium-containing binders is limited, and there is insufficient data to support specific recommendations.[86] Long-term effects on bone and safety profile of lanthanum in children are not yet available, but due to bone deposition and uncertain long-term effects on bone, lanthanum is not recommended in pediatric patients.

Pregnancy

Sucroferric oxyhydroxide (Velphoro) is Pregnancy Category B. Ferric citrate (Auryxia) was previously assigned Pregnancy Category B, but its labeling was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) and now states that there are no adequate and well-controlled studies in pregnant women. It is not known if ferric citrate has the potential to cause fetal harm when administered to a pregnant woman. Its effects on absorption of vitamins has not been studied in pregnancy women. Iron overdose during pregnancy may increase the risk of spontaneous abortion, gestational diabetes, and fetal malformation.

Sevelamer carbonate (Renvela) was previously assigned Pregnancy Category C, but its labeling was updated in compliance with the PLLR. Labeling now states sevelamer carbonate is not absorbed systemically following oral administration and maternal use is not expected to result in fetal exposure; however, use may decrease serum levels of fat soluble vitamins and folic acid in pregnant women, and supplementation should be considered. All other agents in this class are Pregnancy Category C.

DOSAGES[87,88,89,90,91,92,93,94]

Drug	Initial Dosing	Maintenance Dosing	Availability
calcium acetate (Eliphos)	1,334 mg with each meal	2,001 mg to 2,668 mg with each meal	667 mg tablet
calcium acetate*	1,334 mg with each meal	2,001 mg to 2,668 mg with each meal; dose may be titrated every 2 to 3 weeks	667 mg gelcap (capsule)
calcium acetate (Phoslyra)	10 mL with each meal	15 mL to 20 mL with each meal; dose may be titrated every 2 to 3 weeks	667 mg per 5 mL solution
ferric citrate (Auryxia)	Hyperphosphatemia: 2 tablets orally 3 times per day with meals Iron deficiency anemia: 1 tablet orally 3 times per day with meals	Hyperphosphatemia: 8 to 9 tablets per day, up to a maximum of 12 tablets daily; dose may be increased or decreased by 1 to 2 tablets daily over 1 week or longer intervals Iron deficiency anemia: Adjust dose as needed to maintain hemoglobin goal; maximum of 12 tablets per day	210 mg ferric iron (equivalent to 1 g ferric citrate) tablet
lanthanum carbonate (Fosrenol)	1,500 mg in divided doses daily given with or immediately after meals	1,500 mg to 3,000 mg in divided doses daily given with or immediately after meals; doses can be titrated in increments of 750 mg daily every 2 to 3 weeks; doses up to 4,500 mg were evaluated	500 mg, 750 mg, and 1,000 mg chewable tablets 750 mg, 1,000 mg oral powder (brand only) Tablets should be chewed completely; do not swallow intact tablet; consider crushing tablets prior to administration for patients with poor dentition or using the oral powder Oral powder should be sprinkled in applesauce or other similar food and taken immediately; do not attempt to dissolve in liquid
sevelamer carbonate (Renvela)	Adults: 800 to 1,600 mg 3 times daily with each meal based on serum phosphorus level Pediatrics ≥ 6 years: 800 mg to 1,600 mg 3 times daily with each meal based on body surface area (BSA)	Adults: 1,600 mg to 2,400 mg 3 times daily with each meal; titrate dose by 800 mg 3 times per day with meals at 2-week intervals; the maximum daily dose is 14 grams Pediatrics ≥ 6 years: titrate dose by 400 mg to 800 mg (increment based on BSA) 3 times per day with meals at 2-week intervals	800 mg tablets 800 mg, 2,400 mg powder packets Powder does not dissolve in water and requires vigorous stirring prior to drinking and should be consumed within 30 minute, resuspend right before drinking

Dosages continued

Drug	Initial Dosing	Maintenance Dosing	Availability
sevelamer hydrochloride (Renagel)	800 mg to 1,600 mg 3 times daily with each meal based on serum phosphorus level	800 mg to 1,600 mg with each meal; dose may be increased or decreased by 1 tablet per meal at 2-week intervals based on serum phosphorus levels; the maximum daily dose is 13 grams	400 mg, 800 mg tablets
sucroferric oxyhydroxide (Velphoro)	500 mg 3 times daily with meals (1,500 mg daily)	1,500 mg to 3,000 mg daily; Titrate dose by 500 mg per day with meals at 1-week intervals	500 mg chewable tablet Tablets must be administered with meals and chewed completely and not swallowed whole; the tablets may be crushed to aid with chewing and swallowing

* Generic for PhosLo by Fresenius Medical Care; the brand has since been discontinued.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance. Many of the trials with agents in this class were performed in an open-label manner; introduction of bias must be considered when evaluating study findings.

calcium acetate (PhosLo) versus sevelamer hydrochloride (Renagel)

In an open-label, randomized trial, calcium acetate and sevelamer hydrochloride were compared for safety and efficacy in controlling hyperphosphatemia in hemodialysis patients.[95] Following a 2-week washout period, 84 patients were randomized to calcium acetate or sevelamer for 8 weeks. Patients were then crossed over to the alternate therapy following an additional 2-week washout period. Doses of both agents were titrated to achieve appropriate phosphate levels. A similar decrease in phosphate levels was observed between the 2 therapies (sevelamer -2 ± 2.3 mg/dL versus calcium acetate -2.1 ± 1.9 mg/dL). Hypercalcemia (serum calcium > 11 mg/dL) was observed in 22% of patients receiving calcium acetate. Five percent of patients receiving sevelamer developed serum calcium > 11 mg/dL (versus calcium acetate; $p<0.01$), and the incidence was not different from the incidence of

hypercalcemia during the washout period. A mean reduction of LDL-C of 24% was observed with sevelamer treatment.

The Calcium Acetate Renagel Evaluation (CARE) study was an evaluation of calcium acetate and sevelamer to see which therapy achieved the treatment goals of phosphorus (≤ 5.5 mg/dL) and the Ca X P product (≤ 55 mg^2/dL^2).[96] One hundred hemodialysis patients were randomized in the double-blind, 8-week trial. Patients treated with calcium acetate achieved lower serum phosphorus (difference of -1.08 mg/dL, p=0.0006), higher serum calcium (difference of +0.63mg/dL, p<0.0001), and lower Ca X P product (difference of -6.1 mg^2/dL^2) than the sevelamer-treated patients based on time-averaged concentrations for weeks 1 to 8. For each week, calcium acetate-treated patients were 20% to 24% more likely to be at goal for phosphate levels and 15% to 20% more likely to be at goal for the Ca X P product. Hypercalcemia was more common with calcium acetate (odds ratio [OR], 6.1; 95% confidence interval [CI], 2.8 to 13.3; p<0.0001). At week 8, intact PTH levels were not significantly different.

ferric citrate (Auryxia) versus placebo for hyperphosphatemia

In a 4-week double-blind, parallel-group study, 192 subjects with CKD, on dialysis and with serum phosphorus between 6.1 and 10 mg/dL, were randomized to ferric citrate 1.5 g, 3 g, or 6 g per day or placebo.[97] The mean change in serum phosphorus reported for placebo, ferric citrate 1.5 g, 3 g, and 6 g groups were 0.04 mg/dL, -1.3 mg/dL, -2.2 mg/dL, and -4.1 mg/dL, respectively. Serum phosphorus levels of ≤ 5.5 mg/dL were reached for 2.5%, 16.7%, 50%, and 92.6% of patients in each group, respectively. Common adverse events reported were gastrointestinal in nature.

ferric citrate (Auryxia) and calcium acetate and/or sevelamer carbonate (Renvela) for hyperphosphatemia

In a long-term, active-control trial, a total of 441 patients with CKD and a serum phosphorus of 7.5 mg/dL during a 2-week washout period were randomized in a 2:1 manner to ferric citrate or an active control, calcium acetate, and/or sevelamer carbonate.[98] Ninety-six percent of patients were on hemodialysis. After randomization, patients either continued the active control drug at the same dose, or started ferric citrate 6 tablets per day, divided with meals. The phosphate binder dose was adjusted to maintain a serum phosphorus level between 3.5 and 5.5 mg/dL, to a maximum of 12 tablets per day. Similar decreases in serum phosphorus were seen in both groups by week 12 and remained through week 52. Following week 52, patients who received ferric citrate were eligible to enter a 4 week placebo-controlled withdrawal phase. Patients were randomized 1:1 to ferric citrate or placebo. Serum phosphorus level continued to decrease in the ferric citrate group by 0.24 mg/dL and increased by 1.8 mg/dL in the placebo group (p<0.0001).

ferric citrate (Auryxia) versus placebo for iron deficiency anemia

A 16-week, randomized, double-blind clinical trial in adults with CKD not on dialysis and iron deficiency anemia compared the safety and efficacy of oral ferric citrate (n=117) and placebo (n=115).[99] The starting dose was ferric citrate 1 g three time daily or matching placebo; doses were titrated to achieve and increase in hemoglobin by > 1 g/dL over baseline. Significantly more patients randomized to ferric citrate achieved the primary endpoint ≥ 1 g/dL increase in hemoglobin at any point during the 16 weeks (52.1% versus 19.1%, respectively; p<0.001). Secondary endpoints were significance improved with ferric citrate, including the mean relative change in hemoglobin (0.84 g/dL; 95% CI, 0.58 to 1.1 g/dL; p<0.001) and the proportion of patients who achieved a sustained increase in hemoglobin (≥ 0.75

g/dL over any 4-week period during the randomized trial; 48.7% versus 14.8%, respectively; p<0.001). Incidence of serious adverse events were similar between the groups (ferric citrate, 12%; placebo, 11.2%). Gastrointestinal disorders were the most common adverse events (diarrhea, 20.5% versus and 16.4%, respectively; constipation, 18.8% versus 12.9%, respectively, in the ferric citrate and placebo groups).

lanthanum (Fosrenol) versus calcium carbonate

In a phase 3, open-label study, lanthanum and calcium carbonate were compared for the effects on renal osteodystrophy in 98 dialysis patients.[100] Patients were randomized to lanthanum or calcium carbonate following a baseline bone biopsy. Bone biopsies were also evaluated after 1 year. Periodic assessments of electrolytes and adverse effects were recorded. At 1 year, 63 sets of bone biopsies were available. Serum phosphate was well controlled in both groups. Hypercalcemia was reported less often with lanthanum than calcium carbonate (6% and 49%, respectively). Subtypes of renal osteodystrophy at baseline were similar in both groups with the mixed type being most common. The percentage of patients with adynamic bone, osteomalacia, or hyperparathyroidism was reduced by lanthanum therapy from 36% to 18% over 1 year. The calcium group saw an increase from 43% to 53% of patients with evidence of adynamic bone, osteomalacia, or hyperparathyroidism after 1 year. No aluminum-type effects on bone were seen with lanthanum use. Adverse effects were mostly GI in nature. Both groups had similar discontinuation rates.

A randomized, open-label trial compared lanthanum and calcium carbonate for control of serum phosphate levels over 20 weeks.[101] Patients (n=800) underwent a washout period and then were randomized to lanthanum or calcium carbonate. Patients completed a 5-week dose titration period. Control of phosphate levels (≤ 5.58 mg/dL) was achieved by 65.8% and 63.9% of lanthanum- and calcium-treated patients, respectively, during 20 weeks of active treatment. Hypercalcemia was reported in 20.2% of calcium-treated patients compared to 0.4% of patients receiving lanthanum. The Ca X P product was slightly better controlled with lanthanum. The most common daily dose of lanthanum was 1,500 mg with a range of 375 to 3,000 mg per day. The most frequently used calcium carbonate daily dose was 3,000 mg (1,200 mg elemental calcium) with a range of 1,500 to 9,000 mg per day.

The above evaluation by Hutchinson and colleagues was extended an additional 6 months and then 2 years.[102] Patients on lanthanum continued the maintenance dose as established in the previous study. Patients originally assigned to the calcium group were switched to lanthanum and underwent dose titration over 5 weeks. A total of 518 patients entered the 6-month extension. Mean serum phosphorus throughout the 6-month study extension was 5.5 mg/dL and 5.7 mg/dL in the lanthanum group and the group that switched from calcium to lanthanum, respectively. Hypercalcemia was reported in 2.7% of patients. A total of 161 patients entered the 2-year extension phase; patients underwent a dose titration to achieve acceptable phosphorus control. Ninety patients completed the 2 years, and 46 of the patients were from the original lanthanum group. At the end of 2 years, 59% of the 90 remaining patients had serum phosphorus levels ≤ 5.6 mg/dL. The most common adverse events were GI related.

lanthanum (Fosrenol) versus sevelamer hydrochloride (Renagel)

A crossover study evaluated lanthanum and sevelamer hydrochloride in the reduction of serum phosphorus in hemodialysis patients.[103] This study began with an initial 2- to 3-week washout period, followed by randomization to either lanthanum (2,250 to 3,000 mg/day) or sevelamer (4,800 to 6,400 mg/day). Patients completed 4 weeks of the initial therapy before a second washout period and

conversion to the alternative product. While lanthanum was shown to reduce serum phosphorus by 1.7 mg/dL, compared with 1.4 mg/dL for sevelamer, this difference was not statistically significant in the primary analysis. Lanthanum did demonstrate a significantly greater reduction in a pre-specified secondary analysis of patients who completed 4 weeks of treatment with each of the products. It was also noted that the reduction in serum phosphorus was greater with lanthanum after the initial week of treatment (p=0.024).

sevelamer hydrochloride (Renagel) and calcium therapy

An open-label study evaluated 55 hemodialysis patients to determine the effects of sevelamer hydrochloride with and without calcium supplementation on serum phosphorus, calcium, and PTH.[104] Patients were randomized following a 2-week washout period to sevelamer or sevelamer with 900 mg of elemental calcium daily on an empty stomach. Forty-nine percent of all patients were also taking vitamin D metabolites. Efficacy of treatment in reducing serum phosphorus was similar for both groups. An insignificant increase in serum calcium occurred in the sevelamer plus calcium group. Non-users of vitamin D metabolites randomized to sevelamer plus calcium had a significant decrease in PTH (p=0.006) compared to sevelamer therapy alone. The sevelamer plus calcium group showed decreasing PTH levels throughout the study. All therapies were well tolerated.

sevelamer hydrochloride (Renagel) versus calcium therapy

The Dialysis Clinical Outcomes Revisited (DCOR) study was an open-label, prospective, randomized, controlled, 3-year trial comparing sevelamer and calcium-based phosphate binders (PhosLo or calcium carbonate) for all-cause mortality and cause-specific mortality (cardiovascular mortality, infection, and other causes) in 2,103 patients.[105] Patients were followed for up to 45 months. Forty-three percent of patients enrolled were followed for more than 2 years, and 1,068 patients completed the study. Seventy percent of the calcium group took PhosLo tablets; the remaining 30% took calcium carbonate. The mean prescribed dose was 5.3 g calcium acetate, 4.9 g calcium carbonate, and 6.9 g sevelamer. The primary endpoint was all-cause mortality, and no difference between the 2 groups was observed (relative risk, 0.93; 95% CI, 0.79 to 1.1; p=0.4). An evaluation of patients who completed at least 2 years in the study (43%) revealed a difference in all-cause mortality favoring sevelamer (p=0.02). Deaths were reported in 26 (n=142) and 27 (n=147) percent of the sevelamer and calcium-based groups, respectively. Overall cardiovascular mortality (p=0.53) was similar between the 2 groups. When evaluating cardiovascular mortality and age (> 65 years or < 65 years), all-cause mortality and cardiovascular mortality were both significantly lower with sevelamer in the older population compared to the calcium group (both p=0.02). The time-weighted mean serum calcium values, total cholesterol, and LDL-C values were significantly lower in the sevelamer group (all p<0.0001). The Ca X P product was similar in both groups (p=0.6).

As a secondary analysis, hospitalization and cardiovascular morbidity were extracted from a merger of the DCOR study patient data and the Centers for Medicare and Medicaid Services (CMS) ESRD database.[106] Patients included in the analysis used Medicare as the primary payer for treatment. Outcome parameters and cardiovascular comorbidity assessments were derived from Medicare claims data. A greater percentage of calcium-treated patients had atherosclerotic heart disease. Sevelamer had a positive effect on hospitalization days (p=0.009) and the multiple hospitalization rates (p=0.046) compared to the calcium-based binder group. No significant effect was seen in all-cause hospitalization rate or cardiovascular morbidity over the study time frame. Early discontinuation was similar in both

groups (sevelamer n=502; calcium n=533, p=0.15). The lead author disclosed support from the manufacturer of sevelamer.

A randomized (1:1), 36 month, open-label, multicenter study was performed to assess the impact of sevelamer hydrochloride (n=232) versus calcium carbonate (n=234) on cardiovascular death due to arrhythmias, all-cause cardiovascular death, and all-cause death in adult patients (n=466) with CKD stage 5 new to hemodialysis.[107] The average doses of sevelamer and calcium were 4,300 ± 1,400 mg (median 4,800 mg) daily and 2,200 ± 1,000 mg (median 2,000 mg) daily, respectively, and investigators were allowed to adjust dosing, as needed, in order to achieve a serum phosphorus level of 2.7 to 5.5 mg/dL. At the conclusion of the study, patients treated with sevelamer (4.2 ± 1.2; -1.37 ± 1.93 change from baseline; p<0.001) had lower serum phosphate levels compared to patients treated with calcium carbonate (4.8 ± 1.1; -0.1 ± 1.67 change from baseline; p=0.4). Patients were monitored for up to 36 months and 128 deaths were reported at follow up. The study concluded that sevelamer-treated patients had a substantial reduction in risk of cardiovascular death due to cardiac arrhythmias (p<0.001) compared to calcium treated patients. There were 2 and 27 patients who had cardiovascular deaths due to cardiac arrhythmias in the sevelamer and calcium group, respectively, which correlates with a greater than 10-fold reduction in risk for experiencing a lethal arrhythmia (hazard ratio [HR], 0.06; 95% CI, 0.01 to 0.25; p<0.001). Likewise, 9 and 80 patients suffered from an all-cause cardiovascular death in the sevelamer and calcium treated group, respectively, which also correlates with a 10-fold risk reduction (HR, 0.09; 95% CI, 0.05 to 0.19; p<0.001). All-cause mortality was also reduced in the sevelamer treated patients (p<0.001). Overall, the study concluded that sevelamer reduces cardiovascular and all-cause mortality in patients with CKD stage 5.

sevelamer hydrochloride (Renagel) versus sevelamer carbonate (Renvela)

In a double-blind, randomized, cross-over trial, sevelamer carbonate and sevelamer hydrochloride were compared in 79 hemodialysis patients for effects on serum phosphorus, lipids, and bicarbonate levels.[108] Patients received 8 weeks of treatment followed by 8 weeks of the alternative treatment. The mean serum phosphorus was 4.6 ± 0.9 mg/dL and 4.7 ± 0.9 mg/dL during sevelamer carbonate and sevelamer hydrochloride treatment, respectively. Mean total cholesterol and LDL-C were 144 mg/dL and 59.5 mg/dL, respectively, during sevelamer carbonate treatment and 139 mg/dL and 56 mg/dl, respectively, during sevelamer hydrochloride treatment. Serum bicarbonate levels increased by 1.3 mEq/L during sevelamer carbonate treatment. Fewer gastrointestinal adverse events were observed with sevelamer carbonate.

Another randomized, parallel, open-label study evaluated once-daily sevelamer carbonate powder for oral suspension versus 3-times daily sevelamer hydrochloride tablets in hemodialysis patients.[109] After an initial 2-week washout, patients were randomly assigned to 1 of these therapies and evaluated for change in serum phosphorus levels from baseline to 24 weeks after therapy initiation. Phosphorus level decreased 2 ± 1.8 mg/dL for sevelamer carbonate and 2.9 ± 1.3 mg/dL for sevelamer hydrochloride (p<0.001). Adverse event rates were similar between the groups with a greater percentage of treatment-related upper gastrointestinal events occurring with the carbonate product.

sucroferric oxyhydroxide (Velphoro) versus sevelamer hydrochloride (Renagel)

A randomized clinical trial was performed to determine the ability of sucroferric oxyhydroxide in lowering serum phosphorus in patients with ESRD on dialysis.[110] In the first study, 154 patients with ESRD on hemodialysis having elevated levels of serum phosphorus (> 5.5 mg/dL but < 7.75 mg/dL)

were randomized to receive sucroferric oxyhydroxide at 250 mg; 1,000 mg; 1,500 mg; 2,000 mg; or 2,500 mg daily or active-control (sevelamer HCL) after a 2-week phosphate binder washout period. Sucroferric oxyhydroxide treatment was divided across meals and no dose titration was allowed. At the end of the study, serum phosphorus levels were compared to baseline values and it was found that sucroferric oxyhydroxide was efficacious ($p \leq 0.016$) for all doses, with the exception of the 250 mg daily dose. Sucroferric oxyhydroxide also had similar GI adverse event profiles compared to sevelamer HCL and no dose-dependent GI trend events were observed.

sucroferric oxyhydroxide (Velphoro) versus sevelamer carbonate (Renvela)

In a clinical study, 1,054 patients with elevated serum phosphorus levels (≥ 6 mg/dL), following a 2- to 4-week phosphate binder washout phase and on hemodialysis (n=968) or peritoneal dialysis (n=87), were randomized to receive 1,000 mg daily of sucroferric oxyhydroxide (n=707) or active control (sevelamer carbonate, n=348) for 24 weeks.[111] At the end of 24 weeks, patients on hemodialysis (n=93) whose serum phosphorus levels were controlled (< 5.5 mg/dL) with sucroferric oxyhydroxide were re-randomized to receive a maintenance dose of sucroferric oxyhydroxide (n=44) or a non-effective dose (250 mg daily, n=49) for an additional 3 weeks. At the end of week 27, the study showed that sucroferric oxyhydroxide (1,000 to 3,000 mg daily) was statistically significantly superior ($p<0.001$) in maintaining a mean lower serum phosphorus level compared to the low dose control, 5 mg/dL versus 6.8 mg/dL, respectively. Following the completion of the study, 658 patients were treated in the 28-week extension study with sucroferric oxyhydroxide (n=391) or sevelamer carbonate (n=267) according to the patient's original randomization. The patients' serum phosphorus levels declined during the first few weeks and then remained consistent through 12 months of treatment. Serum iron level increases from baseline were not clinically significant, did not differ significantly from the active control, and did not accumulate during the year of treatment. Similarly, there were no clinically significant changes in vitamins A, D, E, and K when using sucroferric oxyhydroxide.

META-ANALYSES

A systematic review evaluated the effect of calcium-based (calcium carbonate or calcium acetate) versus non-calcium-based phosphate binders (sevelamer hydrochloride, sevelamer carbonate, or lanthanum) on mortality in patients with chronic kidney disease.[112] Randomized and non-randomized trials from August 2008 through October 2012 were retrieved from numerous databases, examined, and combined with a previous meta-analysis for assessment of outcomes. The primary outcome assessed was all-cause mortality and the secondary outcomes assessed were cardiovascular events (fatal and non-fatal stroke; fatal and non-fatal myocardial infarction; and sudden death), vascular calcification, vascular compliance, and fractures. Eight new studies (4 open-label randomized controlled trials, 2 observational cohort studies; 1 blinded randomized controlled trial; and 1 cross-sectional study) were added to the 10 studies from a previous meta-analysis and included 3,230 participants (1,726 received calcium carbonate or calcium acetate; 774 received sevelamer; and 730 received lanthanum). Eleven randomized studies (n=4,622) were used to assess all-cause mortality and showed a 22% reduction in all-cause mortality in patients receiving non-calcium based phosphate binders compared to those taking calcium-based therapy (risk ratio 0.78, 95% CI, 0.61 to 0.98). Furthermore, follow-up at 24 months indicated a significant reduction in mortality in patients taking non-calcium based phosphate binders compared to patients taking calcium-based phosphate binders. Patients taking calcium-based phosphate binders had increased coronary artery calcification compared

to patients taking non-calcium based phosphate binders. A subgroup analysis to determine whether mortality varied by type of non-calcium based phosphate binder showed a statistically non-significant decrease in mortality in patients taking either sevelamer or lanthanum compared to patients taking calcium-based phosphate binders. Limitations of the review include the fact that no new studies examined cardiovascular mortality so the review cannot distinguish between CV mortality and other types of mortality on the basis of type of phosphate binder used. Sucroferric oxyhydroxide was not available at the time of this meta-analysis.

A network meta-analysis compared the efficacy of different phosphate lowering strategies, including various calcium salts, sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, sucroferric oxyhydroxide, and ferric citrate, on laboratory outcomes (29 studies, n=8,335).[113] No significant differences were found between active treatment categories and serum phosphate; however, sevelamer and lanthanum were more effective than calcium.

Another network meta-analysis of 77 clinical trials compared the effect of various phosphate binders, including sevelamer, lanthanum, calcium, and other agents not included in this therapeutic class, on all-cause mortality (n=12,562).[114] No evidence was found that phosphate binder treatment reduces mortality compared to placebo in adults with CKD; however, all treatments were found to be superior to placebo in lowering serum phosphorus. Compared to one another, there were few differences in mortality, although a statistical difference was found favoring sevelamer over calcium based on very limited data with short follow-up (odds ratio [OR], 0.39; 95% CI, 0.21 to 0.74).

SUMMARY

Chronic kidney disease (CKD) is a prevalent disease state in the United States impacting over 30 million Americans. As kidney function deteriorates, the levels of phosphorus increase which results in hyperphosphatemia. Hyperphosphatemia can lead to severe complications, such as renal bone disease and soft tissue calcification, including cardiac and vasculature tissue calcification, and increase the risk of death. Studies have shown that control of hyperphosphatemia through dietary phosphorus management, dialysis, and phosphate binders is critical in the prevention and delay of renal osteodystrophy and soft tissue calcifications. The KDIGO guidelines do not strongly prefer 1 type of phosphate binder over another for adults and have noted that the selection of an appropriate phosphate binder should be individualized and based on various clinical parameters, not phosphorus lowering alone.

Phosphate-binding therapy with calcium acetate (PhosLo generics, Eliphos, and Phoslyra) is as effective as sevelamer (Renagel, Renvela) in reducing serum phosphate levels. Sucroferric oxyhydroxide (Velphoro) has also shown phosphate lowering capabilities when compared to sevelamer HCl and sevelamer carbonate without causing a clinically significant iron accumulation. Ferric citrate (Auryxia) was also shown to similarly decrease serum phosphorus levels compared to calcium acetate and/or sevelamer carbonate (Renvela). Sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela) have been compared in 1 trial which demonstrated similar efficacy. However, increased serum bicarbonate levels were observed in the serum carbonate (Renvela) group compared to the sevelamer hydrochloride group (Renagel).

Unlike other agents, hypercalcemia occurs more frequently with calcium acetate (PhosLo generics, Eliphos, and Phoslyra) in a small portion of patients. However, calcium supplementation may be required with sevelamer (Renagel, Renvela) to enhance control of secondary hyperparathyroidism.

Lanthanum (Fosrenol) is another non-calcium, non-aluminum, phosphate-binding agent. The long-term effects of lanthanum (Fosrenol) on bone remain unclear.

In conclusion, all phosphate binders are efficacious in reducing serum phosphate levels; one product has not been found to be superior over another and therapy should be individualized to meet the patient's unique medical needs.

Iron deficiency anemia is often associated with CKD and can lead to increased mortality and cardiovascular events. Ferric citrate (Auryxia) is also indicated as an iron replacement product for the treatment of iron deficiency anemia in adults with CKD who are not on dialysis.

REFERENCES

1 Eliphos [package insert]. Madison, MS; Hawthorn; August 2016.
2 PhosLo [package insert]. Waltham, MA; Fresenius; March 2013.
3 Phoslyra [package insert]. Waltham, MA; Fresenius; October 2015.
4 Auryxia [package insert]. New York, NY; Keryx; November 2017.
5 Fosrenol [package insert]. Wayne, PA; Shire; February 2016.
6 Renvela [package insert]. Cambridge, MA; Genzyme; March 2017.
7 Renagel [package insert]. Cambridge, MA; Genzyme; March 2016.
8 Velphoro [package insert]. Waltham, MA; Fresenius; August 2017.
9 National Kidney Foundation. Available at: https://www.kidney.org/atoz/content/about-chronic-kidney-disease. Accessed November 1, 2017.
10 Block GA, Hulbert-Sheraton TE, Levin NW, et al. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Disease. 1998; 31:607-617.
11 Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Society Nephrol. 2005; 16:520-528.
12 Young EW, Albert JM, Satayathum S, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney Int. 2005; 67(3):1179-87.
13 Block GA, Klassen PS, Lazarus JM, et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004; 15:2208-18.
14 KDIGO clinical practice guidelines. Available at: http://kdigo.org/. Accessed November 1, 2017.
15 Raggi P. Effects of excess calcium load on the cardiovascular system measured with electron beam tomography in end-stage renal disease. Nephrol Dial Transplant. 2002; 17:332-335.
16 Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing hemodialysis. N Engl J Med. 2000; 342:1478-1483.
17 Block GA, Hulbert-Shearon TE, Levin NW, et al. Association of serum phosphorus and calcium x phosphorus product with mortality risk in chronic hemodialysis patients: a national study. Am J Kid Dis. 1998; 31:607-617.
18 KDIGO clinical practice guidelines. Available at: http://kdigo.org/. Accessed November 1, 2017.
19 KDIGO clinical practice guidelines. Available at: http://kdigo.org/. Accessed November 1, 2017.
20 Lesley AI, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. AJKD. 2014; 63(5): 713-735. DOI: 10.1053/j.ajkd.2014.01.416. Available at: http://www.ajkd.org/article/S0272-6386(14)00491-0/fulltext#tbl5. Accessed November 1, 2017.
21 Available at: http://www.nephrotech.com/catindex/items/C10-10-2.html. Accessed November 14, 2016.
22 Available at: www.clinicalpharmacology.com. Accessed November 1, 2017.
23 Available at: http://www.nephrotech.com/magnebind400.html. Accessed November 1, 2017.
24 Fishbane S, Delmez J, Suki WN, et al. A randomized, parallel, open-label study to compare once-daily sevelamer carbonate powder dosing with thrice-daily sevelamer hydrochloride tablet dosing in CKD patients on hemodialysis. Am J Kidney Dis. 2010; 55(2): 307-15.
25 KDIGO Clinical Practice Guidelin for Anemia in Chronic Kidney Disease. 2012. Available at: http://kdigo.org/guidelines/anemia-in-ckd/. Accessed November 30, 2017.
26 Eliphos [package insert]. Madison, MS; Hawthorn; August 2016.
27 Fosrenol [package insert]. Wayne, PA; Shire; February 2016.
28 PhosLo [package insert]. Waltham, MA; Fresenius; March 2013.
29 Phoslyra [package insert]. Waltham, MA; Fresenius; October 2015.
30 Renagel [package insert]. Cambridge, MA; Genzyme; March 2016.
31 Renvela [package insert]. Cambridge, MA; Genzyme; March 2017.
32 Velphoro [package insert]. Waltham, MA; Fresenius; August 2017.
33 Auryxia [package insert]. New York, NY; Keryx; November 2017.
34 Available at: www.clinicalpharmacology.com. Accessed November 1, 2017.
35 PhosLo [package insert]. Waltham, MA; Fresenius; March 2013.
36 Eliphos [package insert]. Madison, MS; Hawthorn; August 2016.
37 Phoslyra [package insert]. Waltham, MA; Fresenius; October 2015.
38 Fosrenol [package insert]. Wayne, PA; Shire; February 2016.
39 Renagel [package insert]. Cambridge, MA; Genzyme; March 2016.

40 Renvela [package insert]. Cambridge, MA; Genzyme; March 2017.
41 Velphoro [package insert]. Waltham, MA; Fresenius; August 2017.
42 Auryxia [package insert]. New York, NY; Keryx; November 2017.
43 Pennick M, Dennis K, Damment SJP. Absolute bioavailability and disposition of lanthanum in healthy human subjects administered lanthanum carbonate. J Clin Pharmacol. 2006; 46:738-746.
44 PhosLo [package insert]. Waltham, MA; Fresenius; March 2013.
45 Eliphos [package insert]. Madison, MS; Hawthorn; August 2016.
46 Renagel [package insert]. Cambridge, MA; Genzyme; March 2016.
47 Renvela [package insert]. Cambridge, MA; Genzyme; March 2017.
48 Fosrenol [package insert]. Wayne, PA; Shire; October 2012 February 2016.
49 Phoslyra [package insert]. Waltham, MA; Fresenius; October 2015.
50 Velphoro [package insert]. Waltham, MA; Fresenius; August 2017.
51 Auryxia [package insert]. New York, NY; Keryx; November 2017.
52 Eliphos [package insert]. Madison, MS; Hawthorn; August 2016.
53 PhosLo [package insert]. Waltham, MA; Fresenius; March 2013.
54 Phoslyra [package insert]. Waltham, MA; Fresenius; October 2015.
55 Fosrenol [package insert]. Wayne, PA; Shire; February 2016.
56 Renagel [package insert]. Cambridge, MA; Genzyme; March 2016.
57 Renvela [package insert]. Cambridge, MA; Genzyme; March 2017.
58 Velphoro [package insert]. Waltham, MA; Fresenius; August 2017.
59 Auryxia [package insert]. New York, NY; Keryx; November 2017.
60 Burke SK, Amin NS, Incerti C, et al. Sevelamer hydrochloride (Renagel), a phosphate-binding polymer, does not alter the pharmacokinetics of two commonly used antihypertensives in healthy volunteers. J Clin Pharmacol. 2001; 41(2):199-205.
61 Burke SK, Amin NS, Incerti C, et al. Sevelamer hydrochloride (Renagel), a nonabsorbed phosphate-binding polymer, does not interfere with digoxin or warfarin pharmacokinetics. J Clin Pharmacol. 2001; 41(2):193-8.
62 How PP, Fischer JH, Arruda JA, et al. Effects of lanthanum carbonate on the absorption and oral bioavailability of ciprofloxacin. Clin J Am Soc Nephrol. 2007; 2(6):1235-40.
63 Eliphos [package insert]. Madison, MS; Hawthorn; August 2016.
64 PhosLo [package insert]. Waltham, MA; Fresenius; March 2013.
65 Phoslyra [package insert]. Waltham, MA; Fresenius; October 2015.
66 Auryxia [package insert]. New York, NY; Keryx; November 2017.
67 Fosrenol [package insert]. Wayne, PA; Shire; February 2016.
68 Renagel [package insert]. Cambridge, MA; Genzyme; March 2016.
69 Renvela [package insert]. Cambridge, MA; Genzyme; March 2017.
70 Velphoro [package insert]. Waltham, MA; Fresenius; August 2017.
71 PhosLo [package insert]. Waltham, MA; Fresenius; March 2013.
72 Behets GJ, Verberckmoes SC, D'Haese PC, et al. Lanthanum carbonate: a new phosphate binder. Curr Opin Nephrol Hypertens. 2004; 13(4):403-9.
73 Fosrenol [package insert]. Wayne, PA; Shire; February 2016.
74 Spasovski GB, Sikole A, Gelev S, et al. Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year of treatment with lanthanum carbonate and after 2 years of follow-up. Nephrol Dial Transplant. 2006; 21(8):2217-24.
75 Fosrenol [package insert]. Wayne, PA; Shire; February 2016.
76 Hutchison AJ, Barnett ME, Krause R, et al for the SPD405-309 Lanthanum Study Group Collaborators. Long-term efficacy and safety profile of lanthanum carbonate: results for up to 6 years of treatment. Nephron Clin Pract. 2008; 110(1):c15-23.
77 Auryxia [package insert]. New York, NY; Keryx; November 2017.
78 Eliphos [package insert]. Madison, MS; Hawthorn; August 2016.
79 PhosLo [package insert]. Waltham, MA; Fresenius; March 2013.
80 Fosrenol [package insert]. Wayne, PA; Shire; February 2016.
81 Phoslyra [package insert]. Waltham, MA; Fresenius; October 2015.
82 Renagel [package insert]. Cambridge, MA; Genzyme; March 2016.
83 Renvela [package insert]. Cambridge, MA; Genzyme; March 2017.
84 Velphoro [package insert]. Waltham, MA; Fresenius; August 2017.
85 Auryxia [package insert]. New York, NY; Keryx; November 2017.
86 Uhlig K, Berns JS, Kestenbaum B, et. Al. KDOQI US Commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD–Mineral and Bone Disorder (CKD-MBD). American Journal of Kidney Disease. 2010; 55(5): 773-799.
87 Eliphos [package insert]. Madison, MS; Hawthorn; August 2016.
88 PhosLo [package insert]. Waltham, MA; Fresenius; March 2013.
89 Phoslyra [package insert]. Waltham, MA; Fresenius; October 2015.
90 Auryxia [package insert]. New York, NY; Keryx; November 2017.
91 Fosrenol [package insert]. Wayne, PA; Shire; February 2016.
92 Renagel [package insert]. Cambridge, MA; Genzyme; March 2016.
93 Renvela [package insert]. Cambridge, MA; Genzyme; March 2017.
94 Velphoro [package insert]. Waltham, MA; Fresenius; August 2017.
95 Bleyer AJ, Burke SK, Dillon M, et al. A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. Am J Kidney Dis. 1999; 33(4):694-701.
96 Qunibi WY, Hootkins RE, McDowell LL, et al. Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate Renagel Evaluation (CARE Study). Kidney Int. 2004; 65(5):1914-26.

97 Yokoyama K, Hirakata H, Akiba T, et al. Effect of oral JTT-751 (ferric citrate) on hyperphosphatemia in hemodialysis patients: results of a randomized, double-blind, placebo-controlled trial. Am J Nephrol. 2012; 36(5):478-87. DOI: 10.1159/000344008.
98 Auryxia [package insert]. New York, NY; Keryx; July 2015.
99 Fishbane S, Block GA, Loram L, et al. Effects of Ferric Citrate in Patients with Nondialysis-Dependent CKD and Iron Deficiency Anemia. J Am Soc Nephrol. 2017;28(6):1851-1858. doi: 10.1681/ASN.2016101053.
100 D'Haese PC, Spasovski GB, Sikole A, et al. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. Kidney Int Suppl. 2003; 85:S73-8.
101 Hutchinson AJ, Maes B, Vanwalleghem J, et al. Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: a 6-month, randomized, comparative trial versus calcium carbonate. Nephron Clin Pract. 2005; 100(1):c8-19.
102 Hutchinson AJ, Maes B, Vanwalleghem J, et al. Long-term efficacy and tolerability of lanthanum carbonate: results from a 3-year study. Nephron Clin Pract. 2006; 102(2):c61-71.
103 Sprague SM, Ross EA, Nath SD, et al. Lanthanum carbonate vs. sevelamer hydrochloride for the reduction of serum phosphorus in hemodialysis patients: a crossover study. Clin Nephrol. 2009; 72(4):252-8.
104 Chertow GM, Dillon M, Burke SK, et al. A randomized trial of sevelamer hydrochloride (Renagel) with and without supplemental calcium. Strategies for the control of hyperphosphatemia and hyperparathyroidism in hemodialysis patients. Clin Nephrol. 1999; 51(1):18-26.
105 Suki W, Zabaneh R, Cangiano J, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney Int. 2007; 72(9):1130-7.
106 St Peter WL, Liu J, Weinhandl E, et al. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. Am J Kidney Dis. 2008; 51(3):445-54.
107 Di lorio B, Molony D, Bell C, et.al. Sevelamer versus calcium carbonate in incident hemodialysis patients: results of an open-label 24-month randomized clinical trial. Am J Kidney Dis. 2013; 62(4):771-778. DOI: 10.1053/j.ajkd.2013.03.023.
108 Delmez J, Block G, Robertson J, et al. A randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis. Clin Nephrol. 2007; 68(6):386-91.
109 Fishbane S, Delmez J, Suki WN, et al. A randomized, parallel, open-label study to compare once-daily sevelamer carbonate powder dosing with thrice-daily sevelamer hydrochloride tablet dosing in CKD patients on hemodialysis. Am J Kidney Dis. 2010; 55(2): 307-15.
110 Velphoro [package insert]. Waltham, MA; Fresenius; August 2017.
111 Velphoro [package insert]. Waltham, MA; Fresenius; August 2017.
112 Jamal SA, Vandermeer B, Raggi P, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet. 2013; 382(9900): 1268-1277. DOI: 10.1016/S0140-6736(13)60897.
113 Sekercioglu N, Angeliki Veroniki A, Thabane L, et al. Effects of different phosphate lowering strategies in patients with CKD on laboratory outcomes: a systematic review and NMA. PLoS One. 2017; 12(3): e0171028.DOI: 10.1371/journal.pone.0171028.
114 Palmer SC, Gardner S, Tonelli M, et al. Phosphate-binding agents in adults with CKD: a network meta-analysis of randomized trials. Am J Kidney Dis. 2016; 68(5): 691-702. DOI: 10.1053/j.ajkd.2016.05.015.